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| 08/817,084 | 04/07/97 | KISHIMOTO T | 53466/200 |

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| EXAMINER | |
|---|---|
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| **ART UNIT** | **PAPER NUMBER** |
| 1644 | #11 |

**DATE MAILED:** 04/10/98

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 08/817,084 | Applicant(s) Kishimoto et al |
|---|---|---|
| | Examiner F. Pierre VanderVegt | Group Art Unit 1816 |

☒ Responsive to communication(s) filed on *Jan 22, 1998* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), ~~or thirty days, whichever is longer,~~ from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *19-29* ~~is~~/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *19-29* ~~is~~/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

This application is a 371 of PCT/JP95/01144, which is a continuation-in-part of application S.N. 08/971,997, which is a file wrapper continuation of application S.N. 08/268,520.

The specification on page 1 should be amended to reflect the priority information and status of the priority documents.

Claims 1-18 have been canceled. New claims 24-29 have been added.

Claims 19-29 are currently pending in this application.

1. In view of the declaration of Dr. Mihara and the amendment filed January 22, 1998, **no outstanding rejections are maintained**.

The Mihara declaration was found to be persuasive regarding the enablement of the instant specification for the inhibition by an IL-6 antagonist of synovial cell growth in vivo. The histological staining photographs, attached to the declaration and referred to therein as Figure 3, of the joints of subjects 7 and 9 clearly show a reduction in the proliferation of synovial cells in the IL-6 antagonist treated subjects.

2. **The following new grounds of rejection have been necessitated by Applicant's amendment.**

3. Claims 19-29 may not have the benefit under 35 USC § 120 of the filing date of application S.N. 08/265,520. For example, "a method for inhibiting synovial cell growth", "method of treating chronic rheumatoid arthritis", and "suppresses abnormal growth of synovial cells" were not disclosed in the priority application. Thus, claims 19-29, which recite features not disclosed in the priority application are entitled only to the filing date of PCT/JP95/01144, which is June 7, 1995. See MPEP 201.22.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 24 and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,591,827 (A) in view of Sipe et al (U) and Hirata et al (A4 on form PTO-1449), all of record.

The '827 patent teaches pharmaceutical compositions comprising therapeutically effective amounts of IL-6 antagonists and a pharmaceutically acceptable carrier (Claims 12-20 in particular) for the treatment of human patients with IL-6 related diseases (Abstract in particular), including rheumatoid arthritis (Column 4, lines 3-8 in particular). The '827 patent is silent about divided doses of 1 to 1000 mg each but does teach the presence of a therapeutically effective amount of the IL-6 agonist being comprised in the pharmaceutical compositions. It would have been well within the purview of a skilled artisan to determine such a therapeutically effective amount. The '827 patent does not teach antibodies to IL-6 receptor. The Sipe et al reference teaches that the destruction of joints caused by rheumatoid arthritis (RA) is due in part to the action of destructive cytokines such as IL-1 and IL-6 and can be modulated at multiple points associated with either cytokine action or production (Abstract in particular). Sipe et al further teaches that potential agents for this modulation include anti-cytokine and anti-cytokine receptor antibodies (Abstract in particular). The combined references do not teach monoclonal antibody to IL-6 receptor. Hirata et al teaches a monoclonal antibody (PM1) which binds to an epitope on the IL-6 receptor and blocks the binding of IL-6 to the receptor (Abstract in particular). It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was

made to substitute the PM1 monoclonal antibody taught by Hirata et al for the monoclonal antibodies of the '012 patent for administration in a manner consistent with the '827 patent. One would have been motivated to combine the references with a reasonable expectation of success by the teachings of Sipe et al that monoclonal antibodies to cytokine receptors are effective agents for blocking the destructive action of cytokines in RA and the teachings of the Hirata et al that the PM1 monoclonal antibody is effective for blocking IL-6 binding to the receptor. One would have been motivated to combine the references with a reasonable expectation of success by the teachings of Sipe et al that monoclonal antibodies to cytokine receptors are effective agents for blocking the destructive action of cytokines in RA.

Applicant has traversed rejection based upon these references as they would be applied to newly entered claims 24 and 26-29 based upon two factors. The first factor is that Applicant is claiming domestic priority dating back to the filing date of U.S. application 08/268,520 which June 6, 1994 by virtue of the instant application being a continuation in part of 08/971,977, which is a continuation of the '520 application. However, as stated supra, sufficient support for the instant claims to RA treatment and prevention of synovial cell proliferation, can not be found in the priority documents, which are drawn to anti-IL-6R antibody treatment for the prevention of bone resorption, and Applicant has not pointed out where such support exists within the priority documents. Therefore, as far as the instant claims are concerned, the priority documents can not be considered to antedate the cited prior art references. The second factor over which Applicant has traversed the rejection is that Sipe et al teaches away from the instant invention and that Sipe et al does not teach or suggest that IL-6 ***causes*** rheumatoid arthritis [sic]. The Examiner respectfully disagrees with Applicant's summary of the Sipe et al reference. First of all, there is no need for Sipe et al to suggest that IL-6 causes RA to teach that it is in some way involved in the disease process. It is well known in the art that many cytokines may be involved in a disease process without being causative to the process. Sipe et al clearly teaches in the Abstract "[*a*] ***complex cytokine network perpetuates joint conditions*** *by direct regulation of metalloproteases,* ***by indirect recruitment of cells that secrete degradative enzymes, and by inhibition of reparative processes****. The destructive action of cytokines such as interleukin-1, interleukin-6 and*

*tumor necrosis factor-α can be modulated at multiple points either associated with cytokine production or with cytokine action. Potential agents for cytokine reduction include selective anti-cytokine antibodies,* ***anti-cytokine receptor antibodies****, cytokine receptor antagonist proteins, and soluble and chimeric cytokine receptor molecules*" (emphases added for clarity). It would have been readily apparent to a skilled artisan at the time the invention was made that antagonization of this complex cytokine network of direct and indirect actions at any point could reasonably be expected to exert an effect on the joint condition. Accordingly, Sipe et al does not, in fact, teach away form the claimed invention, but instead invites the combination of references cited here and would have given a person of ordinary skill in the art a reasonable expectation of success for the treatment of RA.

5. Claims 19-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,591,827 (A, of record) in view of Sipe et al (U, of record), Hirata et al (A4, of record), Sack et al (A15 on form PTO-1449 filed September 26, 1997, newly cited) and Mihara et al (A23 on form PTO-1449 filed September 26, 1997, newly cited).

The '827 patent, Sipe et al and Hirata et al have been discussed supra. The combined references do not teach the reduction of synovial cells by treating with anti-IL-6 receptor antibody. Sack et al teaches that IL-6 is closely associated with synovitis, swelling of the synovium, in chronic RA and positively correlated with histological characteristics thereof (Summary in particular). Mihara et al teaches that the presence of excess IL-6 and soluble IL-6 receptor in the synovial fluid stimulates the proliferation of synovial cells (Figure 1 in particular). Mihara et al further teaches that treating IL-6 stimulated synovial cells with anti-IL-6 or anti-IL-6 receptor antibodies effectively reduced the proliferation of the synovial cells (Figure 3 in particular) and concludes that excess production of IL-6 may be involved in the pathogenesis of RA based on its involvement in abnormal proliferation of synovial cells (page 324, last line of "DISCUSSION" in particular). Therefore, treatment with the anti-IL-6 receptor antibodies prevents the stimulation of the synovial cells by IL-6 in the synovium. It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to combine

the teachings of Mihara et al and Sack et al with those of the '827 patent, Sipe et al and Hirata et al with a reasonable expectation of success. One would have been motivated to combine the references for the reasons stated in paragraph 4, supra, and the teachings of Sack et al that IL-6 is associated with synovitis in RA, the teachings of Mihara et al that anti-IL-6 receptor antibodies reduce proliferation of synovial cells and the general knowledge of those of ordinary skill in the art that cell proliferation is a source for a significant portion of the chronic synovitis seen in RA. Therefore, the skilled artisan would conclude through the combination of these references that reduction of the proliferation of synovial cells would result in reduction of synovitis when comprised in a treatment regimen for chronic RA patients.

***Conclusion***

6. Applicant's amendment necessitated the new ground(s) of rejection presented in paragraph 4 of this Office Action and Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on September 26, 1997 prompted the new ground(s) of rejection presented in paragraph 5 of this Office Action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a) and MPEP § 609(B)(2)(I), respectively. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Effective February 7, 1998, the Group and Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1644.

8. Papers related to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax phone number for official documents to be entered into the record for Art Unit 1644 is (703)305-3014. *Communications which are not to be entered into the record, such as proposed amendments, should be clearly marked "DRAFT" and faxed to (703)305-7401.*

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to F. Pierre VanderVegt, whose telephone number is (703)305-6997. The Examiner can normally be reached Monday through Friday from 8:00 am to 4:30 pm ET. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Christina Chan can be reached at (703)308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist, whose telephone number is (703)308-0196.

April 9, 1998
F. Pierre VanderVegt, Ph.D.
Patent Examiner
Art Unit 1644

David A. Saunders

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1644